REMARKS

Applicants respectfully request favorable reconsideration in view of the herewith presented amendment and remarks.

Claims 1-19 are pending in the instant patent application.

The amendment to claim 1 further describes the repressor binding site. Support for the amendment is found throughout the application, for example, the last paragraph at page 5 continuing to page 6. The changes to dependent claims 2, 3, 4 and 5 reflect the changes made in claim 1. Claims 6 and 7 have been altered to further describe the composition of a 'plurality of COUP-TF' sites by adding "comprising an A repeat VI element." The application frequently states that COUP-TF can bind to any of the A elements, for example, first paragraph page 7. Furthermore, the application specifically states that COUP-TF can bind to A repeat VI, page 41 line 21. Claims 9 and 19 have been amended to reflect a method of administering adenovirus. The application supports a method of administering, for example, by stating, "The vectors of the present invention are useful in DNA delivery systems to help curb the production of replication competent adenovirus (RCA), a virus that is dangerous and potentially toxic to a patient receiving it during patient administration." (page 16, lines 22-26). Claim 10 has been changed by further describing the composition of the packaging signal sequence in claim 10 by adding the A repeat VI element. Support for amended claim 10 is found throughout the application, for example, Example 6 at page 41. Dependent claims 11 through 17 have been amended to reflect the changes of claim 1 and claim 10. The amendment adds no new matter to the specification. Therefore, entry of the amendment is respectfully requested.

Response to Claim Rejections Under 35 USC §112

Claims 9 and 19 have been rejected under 35 U.S.C. 112, second paragraph, as being incomplete, "the steps required for the preparation of the virus to be used in claim 9 or 19 are not provided." Applicants respectfully disagree with this rejection. However, in order to expedite prosecution of the instant application, applicants have amended the claims to address the Examiner's concerns. Reconsideration and withdrawal of the §112 rejection is respectfully requested.

Claims 1, 4, 5 and 17 have been rejected under 35 U.S.C. 112, first paragraph, as being enabled only for "a method of regulating adenoviral packaging wherein repression involves the binding of the lac repressor or COUP-TF protein," and non-enabled for "repression of packaging caused by other DNA binding proteins." Applicants respectfully disagree with this rejection.

Applicants respectfully direct the Examiner's attention to the following passages in the instant application in order to point out: (1) how the disclosure provides a rationale for using particular A elements, and (2) how the disclosure provides guidance in determining how other adenovirus packaging repressor proteins work and are configured in the system.

The use of particular A elements, and the number of repeats used, is in consideration of the efficiency of packaging related by the particular A element. The following passage in the disclosure teaches the different packaging efficiencies of the A elements:

> Multimers of different A repeats are able to direct packaging of viral DNA but at different efficiencies (Schmid and Hearing, 1998). Any of the A repeats may serve as a minimal packaging sequence. Preferably these A repeats are used as multimers in a packaging element. A dimer of A repeats V-VII and a hexamer of A repeat I, most preferably as a multimer, serve as the most efficient packaging domains *in vivo*. A hexamer of A repeat II can also be used in the present invention, having a moderate activity. A hexamer of A repeat VI is also a packaging element, albeit a weak element. A repeat VI, when utilized as a multimer, preferably a 12-mer, efficiently directs packaging. (p.22 lines 7-20)

The above passage teaches the rationale for using a particular A element and for using it in a particular configuration. Applicants note that elsewhere in the specification it states that two copies of the minimal packaging sequences are sufficient for packaging. Based upon these passages, one skilled in the art would have sufficient guidance to carry out the invention as claimed.

Applicants also respectfully contend that the disclosure provides guidance in determining how other adenovirus packaging repressor proteins work and are configured in the system. The application teaches how adenovirus packaging repressor protein binding sites are

configured in the system: "The repressor sites may flank the packaging sequence, may be embedded into the packaging sequence or may alternate the packaging sequence." (p6 lines 3-5) Thus, one skilled in the art recognizes that the repressor binding sites must be positioned between, within or surrounding one or more packaging sequences. The disclosure also teaches generally how adenovirus packaging repressor proteins work in the system: In yet another vector embodiment of the present invention, E2F transcription factor binding sites are embedded within a minimal packaging domain. The idea is the same as directly above [*lac* repressor example], i.e. a high affinity binding site for a DNA binding protein is embedded within a minimal packaging domain with the ability to selectively "activate" the repressor...A high affinity E2F inverted binding site is inserted within a minimal packaging domain containing, for example, A repeats V, VI, and VII. In the absence of 6/7 protein expression (this mutant virus is completely viable), E2F binding to the packaging region is weak and thus repression is weak. In the presence of the E4-6/7 protein, E2F binding is stable and with high affinity. Thus, binding of the bona-fide packaging factor is repressed and packaging of the virus is blocked (p. 21, lines 12-35 of the application)

Thus the disclosure teaches that high-affinity DNA binding proteins, by binding DNA adjacent to, within or in between packaging signals, act to interfere with the binding of "bona-fide" packaging factors thereby repressing packaging.

Applicants also respectfully disagree with the Examiner's contention that the use of different repressor sites to repress packaging is unpredictable because of the disparity of repression mediated by COUP-TF and Lac repressor. The disparity of repression mediated by COUP-TF and Lac is directly related to the efficiency of packaging mediated by the particular A element that COUP-TF or Lac was used to repress. In the instant specification, COUP-TF was used to repress the AVI 12-fold multimer and Lac was used to repress the AV-AVII multimer. The specification explicitly states that AV-AVII confers maximal packaging *in vivo* and that AVI confers weak packaging *in vivo*:

> Specifically, AI and AV-AVII constitute strong P complex binding sites and they confer maximal packaging activity *in vivo*...On the other hand, AVI is noted as a weak binding site for P complex *in vivo*, and it serves as a particularly weak packaging domain *in vivo*. (p.24, lines 5-12).

Furthermore, the disparity of repression can also be accounted for by the number of DNA-binding sites located in AV-AVII multimers as compared to AVI multimers. Figure 7 shows that there are three COUP-TF binding sites in an AVI dimer, and that "the A repeat VI packaging signal is a high affinity binding site for COUP-TF binding." (p.22, lines 24-25, emphasis added) In contrast, Figure 10C shows that there is only 1 Lac binding site in a AV-AVII multimer. Thus, the discrepancy between the two examples is clearly described and explained in the specification as due to the use of particular configurations of the A elements. In view of the foregoing remarks, applicants respectfully request reconsideration and withdrawal of the §112 rejection.

Claims 9 and 19 have been rejected under 35 U.S.C. 112, first paragraph, as "the scope of the claims are broad in that no particular disease state is claimed, no method of administration is recited and no specific adenoviral construct is described." Applicants respectfully disagree with this rejection. However, in order to expedite the prosecution of this application, applicants have amended the claims to address the Examiner's concerns. Reconsideration and withdrawal of the §112 rejection is respectfully requested.

Response to Claim Rejections Under 35 USC §102

Claims 6, 7, 10, 11, 12, 13, 14 and 15 have been rejected under 35 U.S.C. 102(b) as being anticipated by Grable et al. (Journal of Virology (1990) 64(5) 2047-2056). Applicants respectfully disagree with this rejection.

Grable does not disclose the presence of COUP-TF binding sites within adenovirus packaging domain. Nowhere in the Grable reference is any teaching or suggestion presented indicating a COUP-TF binding site. The reference does not describe how COUP-TF might bind to an adenovirus vector, nor does it describe to what sequences COUP-TF might bind. Therefore, Grable does not anticipate the invention as claimed. In addition, the Grable reference does not teach or suggest the A repeat VI element, as claimed. In view of the above remarks, applicants assert that Grable does not anticipate the instant claims.

In addition, applicants respectfully disagree with the Examiner's use of the publication of Schmid et al (Journal of Virology (1998), 72(8); 6339-6347) as prior art to conclude that COUP-TF binds to adenovirus packaging sequences. Schmid is NOT prior art to the instant application. The publication date of Schmid et al. is August 1998, which is after the effective filing date of the instant application, *i.e.* April 15, 1998. Thus, the publication Schmid et al. cannot be used for either §102 or §103 rejections. Reconsideration and withdrawal of the §102(b) rejection is respectfully requested.

Claims 10, 11, 12, 13, 14, and 15 have been rejected under 35 U.S.C. 102(b) as being anticipated by Grable et al. (Journal of Virology (1990) 64(5) 2047-2056), because "based on a minimal packaging sequence of 5'-TTTGN$_8$GC-3', the adenovirus sequence disclosed by Grable et al. has at least 3 packaging signal sequences." Applicants respectfully disagree. Although a sequence is described in Figure 2 of Grable et al., the claimed motif is not taught or suggested.

The sequence described in Grable does not teach or suggest the A repeat VI element as claimed. In addition, Grable does not teach or suggest the critical CG dinucleotide that is necessary to the A repeat motif claimed. Therefore, Applicants respectfully assert that the sequence listed in Figure 2 is not a proper basis for a §102 rejection. There is no direction in Grable et al. to conclude that the minimal adenoviral packaging sequence motif is 5'-TTTGN$_8$CG-3', nor does Grable provide any teaching or suggestion that an A repeat VI element is necessary for packaging and/or repression of packaging. In sum, Grable et al. does not teach or suggest the claimed minimal A repeat motif 5'-TTTGN$_8$CG-3' or the A repeat VI element. Reconsideration and withdrawal of the §102(b) rejection is respectfully requested.

Claims 8 and 18 have been rejected under 35 U.S.C. 102(b) as being anticipated by Haj-Ahmed et al. (Journal of Virology (1986) 57(1):267-274). Applicants respectfully disagree with this rejection. Haj-Ahmed does not teach or suggest the A repeat VI element as a binding site for COUP-TF, nor does it teach or suggest this element for packaging. Thus applicants respectfully urge that the rejection is overcome. Reconsideration and withdrawal of the §102(b) rejection is respectfully requested.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

No additional fee is believed to be necessary.

The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 3927-4133US2.

Respectfully submitted

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APPENDIX

1. (amended) A method of regulating adenovirus packaging comprising the steps of:

a. obtaining an adenovirus vector containing an adenovirus packaging repressor binding site, said binding site being located between, within or surrounding an adenovirus packaging sequence; and

b. propagating said vector in the absence of said packaging repressor; and

c. repressing packaging of said vector in the presence of said packaging repressor.

2. (amended) The method of claim 1 wherein the adenovirus packaging repressor is COUP-TF.

3. (amended) The method of claim 1 wherein the adenovirus packaging repressor is *lac* repressor.

4. (amended) The method according to claim 1 wherein the propagating step occurs in a first cell line and the packaging repressing step occurs in a second cell line.

5. (amended) The method according to claim 1 wherein the packaging repressing step occurs in a cell line [is] coinfected with a vector expressing the adenovirus packaging repressor.

6. (amended) An adenovirus vector comprising an adenovirus packaging sequence containing a plurality of COUP-TF binding sites comprising an A repeat VI element.

7. (amended) An adenovirus vector comprising an adenovirus packaging sequence having at least two copies of 5'-TTTGN$_8$CG-3' and a plurality of COUP-TF binding sites, comprising an A repeat VI element.

9. (amended) A method of [treating patients] administering adenovirus comprising the steps of:

a. [administering an adenovirus vector that was prepared using the] encapsidating the adenovirus vector of claim 8, thereby forming an adenovirus; [wherein the heterologous gene expresses a therapeutically effective amount of protein.]

b. isolating said adenovirus;

c. preparing said adenovirus in a pharmaceutically acceptable carrier; and

d. administering said adenovirus to a mammal.

10 (amended) An adenovirus vector containing a packaging signal sequence consisting of at least two copies of 5'-TTTGN8CG-3' and an A repeat VI element.

11. (amended) An adenovirus vector according to claim 10 wherein an adenovirus packaging repressor binding site is embedded in the packaging signal sequence.

12. (amended) An adenovirus vector according to claim 10 wherein an adenovirus packaging repressor binding site[s] flanks the packaging signal sequence.

13. (amended) An adenovirus vector according to claim 10 wherein an adenovirus packaging repressor binding site[s] alternates with the packaging signal sequence.

15. (amended) An adenovirus vector according to claim 14 wherein [a] an adenovirus packaging repressor binding site is located between packaging signal sequences

16. (amended) An adenovirus vector according to claim 11 or 15 wherein the adenovirus packaging repressor binding site is a *lac* repressor site.

17. (amended) An adenovirus vector according to claim 11 or 15 wherein the adenovirus packaging repressor binding site is a E2F binding site.

19. (amended) A method of [treating patients] administering adenovirus comprising the steps of:

a. [administering an adenovirus vector that was prepared using the] encapsidating the adenovirus vector of claim 10, thereby forming an adenovirus; [wherein the heterologous gene expresses a therapeutically effective amount of protein.]

b. isolating said adenovirus

c. preparing said adenovirus in a pharmaceutically acceptable carrier; and

d. administering said adenovirus to a mammal.